REMARKS

Claims 1 - 25 are in this application. Claims 3, 4, 8, 9, 12 and 13 have been amended. These amendments, as discussed below, are fully supported by the application as filed and no new matter has been added. Claims 1, 2, and 15 to 25 are withdrawn.

Applicants preserve all rights to file one or more divisional applications for any subject matter of the withdrawn claims and any subject matter disclosed in this application and not presently claims.

Rejection of claim 8 under 35 USC 112, second paragraph

The Examiner has recognized typographical errors in claim 8. The Applicants thank the Examiner for continuing the examination of this application on the basis of her interpretation of the terms "and or" as "and/or" and "ss; 2" as "β2". Claim 8 has been amended to correct these typographical errors.

It is respectfully submitted that this rejection is now moot.

Rejections under 35 USC 103

The Examiner has rejected claims 3-5 and 9-12 as being obvious over the combination of Carson and Wheeldon and claims 7 and 8 as being obvious over the combination of Carson, Wheeldon and Gauthier (TiPS 2000). Due to the amendment to claim 6 (deletion of BRL-35135) in the previous response this rejection is also extended to that claim. Claims 13 and 14 are rejected as obvious over the combination of Carson and Wheeldon and Cecil.

The Applicants respond to each of these rejections as follows:

Claims 3-5 and 9-12

The Examiner has noted that Carson teaches that heart failure typically begins with an initial insult

impairing systolic function and over time the response to this injury ultimately leads to compromised heart function. Although the Examiner concedes that Carson does not teach administration of β3-adrenoreceptor agonists, this is allegedly taught by Wheeldon which is said to teach the administration of therapeutic amounts of the β3-adrenoreceptor agonist BRL 35135 which leads to increased systolic blood pressure and stroke distance (pages 364-366 of Wheeldon). Based on this, the Examiner considers that a person skilled in the art would consider claims 3-5 and 9-12 obvious in light of the combination of Carson and Wheeldon.

With regard to Wheeldon, the Examiner has rejected the earlier submission that Wheeldon has no bearing on the patentability of the present claims as it does not teach that BRL-35135 is a β3 adrenoceptor agonist in humans. In particular this rejection was because old claims 3-14 defined a method for treatment of an "individual" and an individual is interpreted by the Examiner in a broad sense as an individual of any species. The Examiner goes on to state that it was well known that β3 adrenoceptor expression was widely variant across species. To support that view, the Examiner referred to Gauthier (TiPS 2000) and Gauthier (J. Pharm. Exp. Ther. 290, 687-693; 1999). The Examiner cites further publications as examples that "BRL-35135 and its *in vivo* metabolite BRL-37344 are rodent specific β3 adrenoceptor agonists".

In reply, the Applicants direct the Examiner to the amended claims which are now limited to 'humans' rather than 'individuals'. Support for this amendment can be found, for example, at paragraphs [0051] and [0070] of the present application.

BRL37344 was not known as a human β3 adrenergic agonist before the present invention.
As a result of the amendment, the Applicants submit that the Examiner's reasoning as to the obviousness of claims 3-5 and 9-12 is no longer applicable at least for the following reason. As acknowledged by the Examiner, before the present invention BRL37344 was not regarded as a human β3 adrenergic agonist but rather only as a rodent specific β3 adrenoceptor agonist. As the Examiner also notes, β3 adrenoceptor expression was understood by those in the art to be widely variant across species. Accordingly, before the present invention the skilled person would not have contemplated use of a rodent specific β3 adrenoceptor agonist in humans.

That BRL37344 was not considered a human β3 adrenergic agonist is apparent on reading Arch page 100, bottom left column (Arch, 2002, Eur J Pharmacol 440; 99-107, submitted with the Information Disclosure Statement accompanying this response) where it is stated that

> identifying highly selective and effective β3 adrenoceptor agonists to selectively stimulate ... β3-adrenoceptor in human tissues is compounded by differences in pharmacology between the rodent and human β3-adrenoceptors, making *in vivo* studies in rodents potentially misleading. Not only do agonists display significant differences in efficacy and potency between rodent and human β3-adrenoceptor, but antagonist potencies may also vary.

The Applicants note that Arch is regarded by those skilled in the art as an authoritative expert on β3 adrenergic pharmacology, and so reinforces the view that the prior art taught away from the invention as now claimed.

The Applicants' position that BRL37344, before the present invention, was not regarded as a human β3 adrenergic agonist is also strongly supported by the 2007 review by Vrydag and Michel (Vrydag and Michel, 2007, Naunyn-Schmiedeberg's Arch Pharmacol 374: 385-398, submitted with the Information Disclosure Statement accompanying this response) which is based on studies published before the filing date the present application. In particular, the Applicants direct the Examiner to the paragraph dedicated to BRL 37344 on page 390-391 of Vrydag and Michel which indicates, amongst other things that "The potency of BRL 37,344 ... was much higher in rats than humans..." and that "The poor subtype selectivity ... of BRL 37,344 seriously limits its usefulness in pharmacological studies."

Further, the Applicants note that after publication of Wheeldon, BRL 35135 essentially disappeared from the art as it pertains to agonism of human β3 adrenergic receptors or administration of β3 agonists to humans. The Applicants submit this is because Wheeldon and previous studies on obesity in humans identified tremor (a classical β2 response) as a side-effect of BRL 35135 administration and no evidence of an effect on the β3 receptor. The Applicants note that Hoffmann 2004 (Naunyn-Schmiedeberg's Arch Pharmacol (2004) 369: 151-159, submitted with the Information Disclosure Statement accompanying this response) specifically studied the selectivity of putative human β3 adrenergic agonists and did not include BRL 35135. The

Applicants submit that this omission and the lack of description of BRL 35135 as a β3 adrenergic agonist in the art after publication of Wheeldon would be seen by a skilled person as indicating that BRL 35135 and thus, using the Examiner's words, "its *in vivo* metabolite BRL-37344" were not known as human β3 adrenergic agonists before the present application.

Carson and Wheeldon: Increased heart rate decreases contractility of failing myocardium

Wheeldon states that BRL35135 "produces most, if not all of its cardiac effects by β2-adrenoceptor stimulation" and merely proposes that a portion of its effect on heart rate, as opposed to contractility, is mediated by β3 adrenoceptors. The Applicants submit that if the chronotropic (heart rate) response, with the large increase in heart rate reported by Wheeldon et al, is mediated by the β3 receptors then Wheeldon et al. teaches away from the use of β3 adrenergic agonists in heart failure, particularly when combined with Carson. Carson also teaches that an increase in stimulation frequency (within the physiological range for heart rates) causes an increase in contractility of normal left ventricular myocardium. In contrast, Carson (Figure 6B, page 434) teaches that an increase in stimulation frequency causes a decrease in contractility in failing myocardium.

The Applicants submit that the combination of Carson (increased heart rate decreases contractility in heart failure) and Wheeldon (β3 agonist increases heart rate) suggest to a skilled person that the administration of a β3 agonist to a human with heart failure will decrease the contractility of the already failing heart, thereby exacerbating the condition rather than treating it. Accordingly, the Applicants submit that a skilled person would not have found it obvious to administer a β3 agonist to a human with heart failure in view of Carson and Wheeldon.

Further, the *in vivo* relevance of the *in vitro* findings of Carson is supported by a decrease in left ventricular ejection fraction in patients with heart failure (Carson, Figure 6A). Carson teaches that heart failure is characterized by impaired systolic function (i.e. decreased cardiac contractility) and a falling left ventricular ejection fraction (page 427). The Applicants submit that this further indicates

how the combination of Carson and Wheeldon teaches away from the invention as presently claimed. Following the teaching of Carson and Wheeldon, if the skilled person were to have contemplated administration of a β3 agonist to a human with heart failure they would have been aware that such administration would result in decreased contractility and so would have dismissed such a notion as clearly detrimental to a patient with heart failure.

Present Application: β3 agonists improve function of failing myocardium

The Applicants submit that the different effects of heart rate on cardiac contractility in normal myocardium and failing myocardium is directly relevant to this application. As was the case in Figure 6B of Carson, an increase in stimulation rate increased developed tension of normal human myocardium studied *in vitro* but decreased tension of failing myocardium (see for example Figure 4, page 878, Pieske and Houser, 2003, submitted with the Information Disclosure Statement accompanying this response). The effect of intracellular sodium (Na) levels on contractility accounted for this as it is known that in normal myocardium a modest increase in intracellular Na levels, which occurs via Na influx as a response to increased heart rate, enhances contractility. However, this enhanced contractility is not maintained at ever increasing Na levels as excess intracellular Na decreases contractility. As a consequence, in the failing myocardium where Na levels are raised compared to normal myocardium (see for example, Figure 3, Pieske and Houser, 2003 and paragraph [167] of the present application), further increase in Na levels that occurs with an increase in heart rate actually reduces contractility of the failing myocardium. The present application describes how β3 adrenergic agonists stimulate the Na-K pump and hence enhance Na export from the Na-overloaded myocytes and restore normal physiology to the failing myocardium. Thus, one mechanism by which β3 agonists function in the treatment of heart failure, as disclosed in this application, was not taught or suggested by Carson or Wheeldon taken alone or in combination.

In light of the claim amendments and the foregoing submission the Applicants respectfully submit that the rejection of claims 3-5 and 9-12 as being obvious in light of Carson and Wheeldon should be withdrawn.

Claims 6 to 8

The Examiner is of the opinion that claims 7 and 8 are obvious over the combination of Carson, Wheeldon and Gauthier (TiPS 2000) and as a result of deleting BRL-35135 from claim 6 the rejection is also extended to that claim.

The Examiner states that Gauthier (TiPS 2000) does relate to the ability of BRL37344 to produce a negative inotropic response without involvement of the β_1/β_2 antagonist activity of nadolol thus the reference cannot be said to teach away from the use of BRL37344 as a treatment of heart failure or its administration to people who may be susceptible to heart failure or myocardial hypertrophy. The Examiner is clear in the opinion that Gauthier (TiPS 2000) suggests the efficacy of BRL37344 as a β3 agonist in certain stages of heart failure.

The Examiner notes that given the variation in β3 agonist efficacy across species and the use of the term "individuals" in the claims, a skilled person would have been motivated to arrive at the claimed invention by substituting BRL-35135 as taught by Wheeldon with BRL37344 as taught by Gauthier (TiPS 2000) with a reasonable expectation of success.

Further, the Examiner is of the opinion that Gauthier (TiPS 2000) directly suggests the efficacy of BRL37344 as a β3 agonist in certain ("earlier") stages of heart failure. The Examiner states that Gauthier (TiPS 2000) pertains to the "ability of the β3 agonist BRL37344 to effect the desired negative inotropic response".

Carson and Wheeldon: Increased heart rate decreases contractility of failing myocardium

The Applicants submit that the comments above in relation to Carson and Wheeldon apply also to this rejection. Further, it is a key feature of heart failure that the heart cannot pump as much blood as the body needs and that systolic function is impaired. This is described in Carson and summarized by the Examiner in the first Office Action at the top of page 6. The Applicants also note that the negative inotropic response (i.e. a decrease in contractility) described by Gauthier (TiPS 2000) would not be considered desirable at any stage of heart failure by anyone of ordinary skill in

the art. It would be considered harmful.

Gauthier (TiPS 2000): Teaches away from the present claims

The Examiner rejected the Applicants submission that Gauthier (TiPS 2000) teaches away from the claimed invention on the basis that it merely mentions that β3 receptor agonists "might be more desirable" in the context of heart failure. The Examiner notes that this statement was made in the context of hypothesizing about potential therapeutic developments and suggests that Gauthier's point is that in later stages of heart failure β_1 and β_2 receptors are down-regulated or desensitized while β3 receptors are overexpressed at which point β3 agonists may be useful, thus the Examiner suggests that Gauthier (TiPS 2000) does not rule out therapeutic uses of β3 agonists in heart failure.

The Applicants submit that the direction of the response referred to by Gauthier (negative inotropic effect, i.e. decrease in contractility) teaches away from the present invention. Additionally, Gauthier does not suggest therapeutic administration of a β3 agonist at any stage of heart failure. On the contrary, Gauthier hypothesizes that activation of the β3 receptor by increased levels of endogenous circulating catecholamines "could be viewed as a mechanism that prevents further myocyte damage in early stages of heart failure but that the receptor-mediated effect becomes harmful as heart failure progresses to a later stage". The hypothetical nature of this opinion is clearly set out in the title of the legend of Figure 4, page 430: "Hypothetical role of inotropically...." The specific therapeutic recommendation made by Gauthier relates to choice of β blockers: one that preferentially targets β_1 and β_2 receptors "might be appropriate ... at earlier stages of the disease while non-specific β blockers and/or specific β3 receptor antagonists might be more desirable when β3-adrenoceptor-mediated pathways become maladaptive".

Gauthier 2000 (TiPS): No practical way to identify transition from "early stage" to "late stage" heart failure

There is no recommendation to use a specific β3 agonist in any part of the article by Gauthier 2000 (TiPS), nor is any data presented that would support such a recommendation.

In addition, Gauthier's hypothesis that choice of β blockers could be based on the effects of β3 adrenoceptor-mediated pathways at different stages of disease would have been recognized by the skilled addressee as profoundly flawed. Central to the prospect of any therapeutic benefit arising from that hypothesis is the ability of the treating physician to clearly distinguish different stages of heart failure. Even now that is not easily achieved. In support of that opinion, the Examiner is referred to the European Society of Cardiology (ESC) Guidelines which indicate that the definition and diagnosis of heart failure is not straightforward (see for example, pages 935-937 of the ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008; European Journal of Heart Failure (2008), 933-989, submitted with the Information Disclosure Statement accompanying this response). The "severity" of heart failure is typically classified according to the New York Heart Association criteria that are based on symptoms. However, there is a poor relationship between symptoms and "severity of cardiac function" (page 939 of ESC Guidelines). As a result there is no practical way that any transition from "early stages" to "later stages" of heart failure, as would be required under Gauthier's hypothetical approach, can be reliably identified. As is widely recognized by clinicians, such a transition can be gradual and insidious or there can be rapid decompensation for no apparent reason.

Without an ability to reliably detect the stage when a β3 receptor agonist would be harmful in heart failure, such an agonist would not be considered safe and so would never be approved by regulatory authorities (e.g. FDA) for use in heart failure at any stage. As a consequence, when the cited art is considered in the context of the prevailing understanding prior to the present invention, it cannot be said that a skilled person would consider it obvious to use a β3 receptor as a treatment of human heart failure as set out in the amended claims. In contrast, it is only by the contribution of the present inventors who surprisingly established that β3 receptor agonists stimulate the Na-K pump in cardiomyoctes and increases performance of the failing heart that the skilled addressee is taught that a β3 receptor agonist can be expected to be useful and safe at all times in the heart failure syndrome.

Gauthier and Carson: Conflicting teachings

Gauthier's hypothesis for choice of β blockers on the basis of their ability to block or not block the β3 receptor is based on receptor activation by "increased circulating catecholamines" (TiPS, 2000, page 430, Col 1, line 16). Of these naturally occurring compounds, norepinephrine has a particularly high affinity for the β3 receptor as highlighted in the last lines of Col 2, page 682 and first lines, Col 1, page 683 in the other article by Gauthier referred to by the Examiner (Can. J. Physiol. Pharmacol. 78, 681-90 (2000)) The Applicant submits that this effect of norepinephrine, which forms the basis for the conflict between Gauthier (TiPS) and Carson, is further supported by Hoffmann (Naunyn-Schmiedeberg's Arch Pharmacol (2004) 369: 151-159 submitted with the Information Disclosure Statement accompanying this response) particularly page 157, right column. Hoffmann 2004 also highlights that the β3 adrenergic receptor is activated by norepinephrine and β3 adrenergic receptor is referred to as "the noradrenergic receptor" (The Applicant notes that noradrenaline is the English nomenclature for norepinephrine).

Further, the Applicants submit that data supporting evidence based (i.e. scientifically documented) treatment of heart failure teaches the use of beta-blockers (i.e. beta antagonists). Consequently, before the present application epinephrine and norepinephrine and beta-agonists in general were considered negative factors in heart failure with treatment of heart failure specifically aimed at blocking their effects. In light of this a cornerstone concept in modern cardiology is that raised levels of catecholamines (including norepinephrine) in chronic heart failure cause disease progression. Accordingly, any beneficial effect of norepinephrine invoked by Gauthier is in direct conflict with Carson. Carson summarizes in considerable detail how norepinephrine is viewed as harmful and indeed "toxic" in heart failure on pages 427-431. The Applicants thus submit that the skilled person would not combine the teachings of Carson and Gauthier to arrive at the invention as now claimed.

Gauthier (Can. J. Physiol. Pharmacol.): Teaches away from the present claims

The Examiner has cited Gauthier (Can. J. Physiol. Pharmacol. 78, 681-690; (2000)) in which negative inotropic effects and decreased contractility were said to be observed with several β3 agonists in humans *in vivo* as an indicator that β3 adrenoceptor expression is widely variant across species. On that basis the Examiner considers that a skilled person would naturally select an agonist

suited to the particular species to be treated.

In reference to Gauthier (Can. J. Physiol. Pharmacol. 78, 681-90 (2000)), the Examiner states: "negative inotropic effects and decreased contractility were observed with several β3 agonists in humans in vivo including BRL37344, SR58611A and CL 316,243" (p 682, col. 2). With respect, the Applicants note that use of the term "*in vivo*" in this context is not correct. The relevant paragraph of Gauthier starts with: "In humans, in vivo studies..." However, the studies with BRL37344, SR58611A and CL 316,243 clearly refer to *in vitro* effects - the variable "peak tension" that is measured cannot be determined in vivo. Gauthier's studies are performed using excised heart muscle strips and thus are not performed *in vivo*.

The Applicants submit that Gauthier (Can. J. Physiol. Pharmacol.), particularly Figure 6 therein, indicates that BRL37344 has a negative inotropic effect in normal heart which correlates with a decrease in contractility. This is the opposite to the present application. In particular at paragraph [0167] the present application indicates that in heart failure β3 agonists enhance cardiac performance.

In view of the limitation of the claims to the treatment of humans and the foregoing submissions the Applicants respectfully submit that one of ordinary skill in the art, in view of Carson, would not have been motivated to substitute the "rat" β3 adrenergic agonist BRL35315 as taught by Wheeldon with the "human" β3 adrenergic agonist BRL37344 as taught by Gauthier with reasonable expectation of arriving at the invention as now claimed.

Accordingly, the Applicant respectfully requests withdrawal of this rejection.

Claims 13 and 14

The Examiner notes that claims 13 and 14 fail to recite stabilisation of "chronic" disease rather than acute disease and thus the argument submitted in the earlier response has not been found persuasive.

In reply, the Applicant has amended claims 13 and 14 to be limited to stabilisation of "chronic" disease. In light of this amendment the Applicants respectfully submit that this rejection is now moot.

Accordingly, it is submitted that the claims under consideration all meet the requirements of 35 USC 103 and it is respectfully requested that these rejections be withdrawn.

It is therefore submitted that this application is in order for allowance and an early action to this end is respectfully solicited.

Respectfully submitted,

JANET I. CORD
C/O LADAS & PARRY LLP
26 WEST 61ST STREET
NEW YORK, NEW YORK 10023
REG. NO. 33778
TEL. NO. (212) 708-1935